Chapter 25: Sexual Function and Fertility

25.1: SEXUAL FUNCTION

25.1.1: Evaluate adults for sexual dysfunction after kidney transplantation. *(Not Graded)*

25.1.2: Include discussion of sexual activity and counseling about contraception and safe sex practices in follow-up of adult KTRs. *(Not Graded)*

KTRs, kidney transplant recipients.

Rationale

- Sexual dysfunction is common in men and women KTRs.
- Many patients will not spontaneously report sexual dysfunction.
- Modification of medications may alleviate sexual dysfunction.
- Therapies are available, although less are available for women than men.
- Sexual dysfunction negatively affects quality of life.
- Contraception can help prevent unwanted pregnancies.
- Safe sex practices can help prevent the acquisition of disease.

Sexual dysfunction is frequent in patients with all stages of CKD, particularly among patients with CKD stage 5 or after transplantation (855). Sexual dysfunction in KTRs may have both organic and psychological causes (856–858). The scope of the problem includes erectile dysfunction, decreased libido and lower frequency of intercourse.

Following kidney transplantation, the metabolic milieu improves, and for some patients sexual function improves as well (859). For others, sexual function does not change and may even worsen (860). One study compared sexual function in men and women on hemodialysis, peritoneal dialysis, with patients with rheumatoid arthritis or after transplantation and found that men and women on dialysis had statistically increased incidence of 'hypoactive sexual desire' compared with those after transplantation. Men on hemodialysis had a significantly higher incidence of 'sexual aversion disorder' as well as 'inhibited male orgasm.' In this study, the 'male erectile disorder' did not differ between the dialysis and transplant groups. Overall, the study concluded that sexual dysfunction in dialysis patients was a consequence of lost sexual interest attributable to fatigue (858).

Problems with sexual function are common following kidney transplantation, but the reported prevalence varies. Problems with sexual function in general have been reported in the range of 45–50% (855,861). One survey found that more than 30% reported a problem to be moderate or severe in magnitude (861). There are few studies focused on this issue for women (861). For men, erectile dysfunction can affect quality of life and be associated with anxiety, depression and loss of self-esteem (862). Following transplantation, erectile dysfunction may improve, especially for younger men (862,863). However, for others the problem may not change or may even get worse (862–864). An Egyptian study of 400 male KTRs reported erectile dysfunction in 36% (865). In a study of simultaneous pancreas–kidney transplant recipients, 79% suffered from some degree of erectile dysfunction (866). Transplant surgery may contribute to erectile dysfunction. Diversion of blood from the penile arteries when the internal iliac arteries are used for transplant anastomosis may play a role (863).

Therapy with 5-phosphodiesterase inhibitors may be effective. These agents are helpful for some, but not all patients (864,867). A double-blind crossover RCT of KTRs found that sildenafil was more effective than placebo with respect to erectile function, orgasmic function, intercourse satisfaction and overall satisfaction (868). There was no significant difference with respect to sexual desire in this study (868). Modification of medications may also be useful for patients with erectile dysfunction and/or decreased libido.

Whether to evaluate men with sexual dysfunction, or initiate a trial with a 5-phosphodiesterase inhibitor, is often unclear. When 5-phosphodiesterase inhibitors are prescribed, care must be taken that the patient is hemodynamically stable and that he avoids alpha-adrenergic antagonists. How to counsel and approach therapy in women with sexual dysfunction is less clear.

Follow-up of KTRs should include discussion of sexual activity, and counseling about contraception and safe sex practices, as is true for patients in the general population (and therefore beyond the scope of this guideline). Sexually active patients who are not in long-term monogamous relationships should use latex condoms during sexual contact to reduce their risk for exposure to CMV, HSV, HIV, HPV, HBV, HCV and other sexually transmitted infections. Sexually active KTRs should avoid sexual

practices that could result in oral exposure to feces or genital secretions.

Recommendations for contraception should be made on an individual basis with consideration given to what is most effective, as well as what can actually be used. Concerns regarding intrauterine devices have included the potential for infection, as well as that they may be less effective in transplant recipients (869). Whether current intrauterine devices may be more effective and less risky in this patient population is unknown.

Research Recommendations

- Studies are needed to determine the etiology, diagnosis and treatment of sexual dysfunction in KTRs.

25.2: FEMALE FERTILITY

25.2.1: We suggest waiting for at least 1 year after transplantation before becoming pregnant, and only attempting pregnancy when kidney function is stable with <1 g/day proteinuria. *(2C)*

25.2.2: We recommend that MMF and EC-MPS be discontinued or replaced with azathioprine before pregnancy is attempted. *(1A)*

25.2.3: We suggest that mTORi be discontinued or replaced before pregnancy is attempted. *(2D)*

25.2.4: Counsel female KTRs with child-bearing potential and their partners about fertility and pregnancy as soon as possible after transplantation. *(Not Graded)*

25.2.5: Counsel pregnant KTRs and their partners about the risks and benefits of breastfeeding. *(Not Graded)*

25.2.6: Refer pregnant patients to an obstetrician with expertise in managing high-risk pregnancies. *(Not Graded)*

EC-MPS, enteric-coated mycophenolate sodium; KTRs, kidney transplant recipients; MMF, mycophenolate mofetil; mTORi, mammalian target of rapamycin inhibitor(s).

Background

Female KTRs of child-bearing potential are those who are not peri- or postmenopausal, and those who have a uterus and at least one ovary. There are no prospective studies on the risks of immunosuppressive medications in pregnancies. Evidence that a drug is not safe in pregnancy may come from case reports, or animal studies demonstrating toxicity at doses comparable to those which might be used in humans (normalized to body surface area). In the absence of data, a drug should be presumed to be unsafe, and patients should be treated accordingly.

Rationale

- Fertility is increased in KTRs compared to CKD stage 5 before transplantation.
- Pregnancy and childbirth in KTRs have a high incidence of complications to mother and child.
- Complications of pregnancy and childbirth can be minimized by the use of lower-risk immunosuppressive agents and multidisciplinary care that includes an obstetrician with expertise in managing high-risk pregnancies.

Pregnancies in patients with CKD stage 5 are uncommon (870). However, fertility is improved and often restored after successful kidney transplantation (871,872). The risks of pregnancy and childbirth to both mother and child are higher for KTRs, compared to the general population, but in stable KTRs pregnancies most often have a good outcome. In KTRs with good kidney function, no proteinuria, and well-controlled blood pressure, there is little risk of graft loss (873–876). However, KTRs with reduced kidney function are at higher risk for allograft dysfunction and graft failure (877). There are few published data in KTRs on which to base a safe recommended GFR. Data in the nontransplant population indicate that women with GFR <40 mL/min/1.73 m^2 and proteinuria >1 g/day are at increased risk for a significantly accelerated GFR decrease, as well as low-birth-weight babies (878). These data were used for the recommendations noted above. It is unclear whether or not the same levels apply to KTRs. Cyclosporine levels decline during pregnancy (877). Nevertheless, the incidence of acute rejection during pregnancy appears to be relatively low (877).

An American Society of Transplantation consensus conference recommended that patients wait for 1 year without acute rejection before pregnancy with the proviso that individual circumstances may modify the appropriate time frame to a shorter or longer time period. Each situation needs to be evaluated on a case-by-case basis (879). It was recently reported that pregnancy within the first 2 years following transplantation may increase the risk of graft loss (880). On the other hand, there have been successful pregnancies before the end of the first posttransplant year (872). Some reports suggest that there is a high incidence of hypertension (873) and preeclampsia in pregnant KTRs (881). Deliveries are more likely to be by caesarean section, for medical indications. The transplant kidney is neither affected by, nor does it affect, a vaginal delivery. In

the absence of medical indications, vaginal deliveries are possible (873).

There is also a higher risk to the fetus for pregnancies in KTRs. There is a higher risk of preterm delivery (<37 weeks) and low birth weight (<2500 g) (873,877,882). The fetus, of course, is exposed to potentially teratogenic immunosuppressive agents (882). There are no RCTs indicating which, if any, immunosuppressive agents are safe to use in pregnancy.

Mycophenolate has been reported to cause severe structural malformations. A characteristic phenotype associated with *in utero* exposure to MMF is emerging that includes cleft lip and palate, microtia, and absence of external auditory canals (883–885). Thus, MMF should generally be changed to azathioprine during pregnancy, a practice endorsed by the European Best Practice Guidelines (886). These guidelines suggest a 6-week window after discontinuing MMF and starting azathioprine, before pregnancy is attempted (886). These same concerns should also apply to EC-MPS. Azathioprine is rated by the FDA as category 'D' (i.e. there is evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk). Despite the FDA category D, azathioprine has been used safely over the years in pregnant transplant recipients. It is considered an acceptable immunosuppressant to use in this clinical setting.

In a meta-analysis of the use of CsA during pregnancy, the incidence of major fetal malformations was 4.1% (2.6–7.0%) (877). This was numerically higher than, but not statistically significantly different from, the rate with non-CNIs. Prednisone at doses low enough to prevent thymic aplasia (usually less than 15 mg/day) is safe in pregnant KTRs. High levels of azathioprine and prednisone can be associated with problems that do not occur when they are used at standard doses.

There are few reports of the use of mTORi and pregnancy. The FDA categorizes sirolimus as 'C.' Category C indicates that either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal effects or other) and there are no controlled studies in women, or studies in women and animals are not available (887). The FDA-approved package labeling for sirolimus notes that sirolimus was embryotoxic or fetotoxic in rats at doses 0.2–0.5 of the clinical doses adjusted for body surface area (887). A voluntary registry reported only seven cases of pregnancy in organ transplant recipients receiving sirolimus (885). None were associated with adverse outcomes, although in most the drug was discontinued when pregnancy was discovered. There are case reports of normal-term pregnancies in women receiving sirolimus (888,889). However, in the absence of adequate safety data, it is prudent to avoid mTORi in pregnancy.

An American Society of Transplantation consensus conference concluded that breastfeeding for KTRs is not contraindicated (879). For KTRs who opt to breastfeed, prednisone is likely to be safe (890). Prednisone and azathioprine are detectible in breast milk (891), but there are no data for MMF or sirolimus. CsA is excreted into breast milk and is not recommended in breastfeeding mothers (877).

Research Recommendations

- Observational studies are needed to determine the incidence and complications of pregnancies in KTRs.

25.3: MALE FERTILITY

25.3.1: We suggest that male KTRs and their partners be advised that:
- **male fertility may improve after kidney transplantation *(2D)*;**
- **pregnancies fathered by KTRs appear to have no more complications than those in the general population. *(2D)***

25.3.2: We recommend that adult male KTRs be informed of the possible risks of infertility from mTORi. *(1C)*

25.3.2.1: We suggest that adult male KTRs who wish to maintain fertility should consider avoiding mTORi, or banking sperm prior to mTORi use. *(2C)*

KTRs, kidney transplant recipients; mTORi, mammalian target of rapamycin inhibitor(s).

Rationale

- Male fertility improves in most KTRs, and may become normal.
- Outcomes of pregnancies fathered by KTRs are similar to those of the general population.
- Rapamycin is associated with low sperm counts. The abnormality is reversible with discontinuation of rapamycin.

Chronic kidney disease is associated with impaired spermatogenesis, decreased testosterone production, decreased libido and increased gonadotropins (892). Uremic hypogonadism is reversible in individuals with successful long-term kidney transplantation (893). Studies from the azathioprine as well as CsA eras show that testosterone levels rise after transplantation. Gonadotropins may decrease, but may not normalize, and semen analysis in most KTRs is normal (893–898). Longer time on dialysis prior to

transplantation and kidney dysfunction may be risk factors for those with residual testicular dysfunction (896,899). Testicular biopsies performed after transplantation show significant improvement, with some residual reduction in sertoli cells and spermatogonia (900).

Although it is unclear whether CsA plays a role in male infertility, it is clear that rapamycin can lead to male infertility (893,899). It causes low sperm counts (901–904) by interrupting the stem cell factor/c-kit system that regulates germ cell proliferation, meiosis and apoptosis, consequently inhibiting spermatogenesis (905). The effects of rapamycin appear to be reversible (901–903).

With regards to potential congenital abnormalities, outcomes of pregnancies fathered by male KTRs do not differ from those of the general population (906). These conclusions are based on data from the National Transplant Pregnancy Registry. This registry is voluntary and thus potentially subject to reporting bias. Nevertheless, the data captured by this registry are crucial but limited. Fewer pregnancy outcomes are reported to the registry for men than women.

Research Recommendations

- Observational studies are needed to determine the incidence and complications of pregnancies fathered by KTRs.